Supply Chain Strategies for Adaptive Clinical Trials

Adaptive clinical trials are defined as studies in which accumulating data is used to decide how to modify aspects of the study as it continues, without undermining the validity and integrity of the trial[1]. Giving sponsors the ability to perform planned changes to a trial design while it is still running can result in shorter development timelines and reduced costs. In a 2011 Pharmatimes survey, almost 60 % of respondents reported that adaptive trials reduced trial duration by an average of three months[2]. The ability to reduce the time for which patients receive ineffective treatment is also an important ethical benefit.

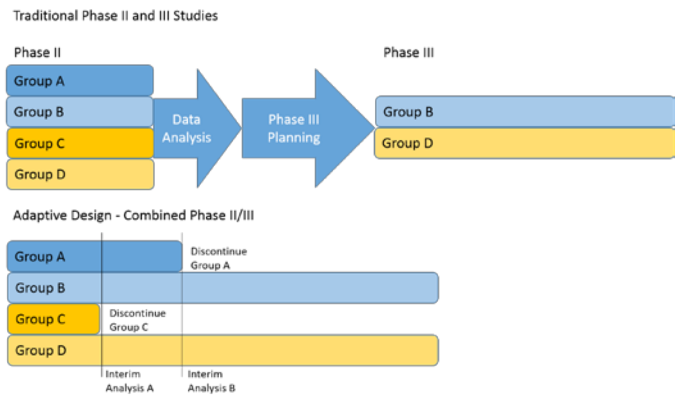


Figure 1: Schematic Showing Traditional vs Adaptive Trial Designs

Despite these advantages, uptake of adaptive designs has remained slow. Recent estimates place uptake at around 20 %, although this is expected to grow rapidly over the next five to ten years, especially in early phase trials. Growth is expected to be fuelled by increasing pressure on sponsors and CROs to reduce study timelines and costs, clearer guidance from regulators (e.g. FDA issued draft guidance on adaptive trial designs in 2010), and the availability of increasingly sophisticated adaptive trial and simulation software . [3]

A key reason for the slow growth of adaptive trial designs has been concerns over the clinical supply chain's flexibility to support demand changes over the course of a clinical trial. If adaptive designs grow as predicted, new thinking is required to manage the risks and costs this could impose on the supply chain. In this paper, we will explore approaches available to help the supply chain to keep pace with changes in demand that adaptive trials may produce.

Changing Times

Current practice in the production of clinical trial medication is to manufacture and package product in as few campaigns as possible, thereby minimising costs associated with operational set-ups and changeovers. Larger-scale operations are also amenable to automation, reducing unit prices. Up-front production of sufficient supplies to cover an entire trial, plus an overage to cover unplanned incidents, helps take clinical supplies off the critical path, reducing the risk of stock-outs at clinical sites.

How does this work with adaptive trials, which can drive increased or decreased sample sizes, add or drop treatment arms, or change allocation ratios of patients to each arm? Mass production of medication up front could result in the supply chain being stocked with too much, or the wrong kind of, medication. By the same token, will it ever be possible to synthesise API, manufacture dose forms and package for clinical trials in short enough timelines to support changes in dosing that may result from adaptive designs? Production of every dose for every scenario 'just in case' goes against the industry's drive for greater supply chain efficiency. Timelines do not support a full supply on demand approach. Solutions therefore must offer a compromise between these two extremes.

Planning

Clinical supply chain planning must ensure that sufficient drug is available at the right dose, in the right place, and at the right time. Historically, our industry guaranteed supply by producing surplus medication (overage). Clinical supplies were considered an insignificant portion of the cost of bringing a new medicine to market, so producing two to three times more stock than a trial required was acceptable. Escalating drug development costs have led to a greater demand for supply chain efficiency, especially given the high unit value of biological innovator and comparator products. Balancing supply with demand is challenging enough for standard trials in which protocols remain fixed for the duration of the study. Adaptive trial designs add to this complexity – some reports estimate that overage figures as high as 500 % are required to support adaptive clinical trials if traditional supply chain planning approaches are employed.[4] Clinical trial planning involves clinical teams, statistics and data management. Supply chain management teams are often involved only when a protocol is at an advanced stage of development. As a result, trials designs may work from a statistical perspective, but may result in a supply chain that is far from optimal. Cross-departmental planning meetings, involving all stakeholders, can help resolve this imbalance.

Simulation tools are increasingly used in clinical trial planning. These allow the impact of various 'what if?' scenarios, and their impact on drug requirements, to be evaluated. Use of simulations is especially important for adaptive trials, in which we *know* changes are likely, to allow planning for all scenarios that could occur. Simulation gives teams a better idea of what to expect if trial designs change so supply strategies can be planned accordingly.

Manufacturing Strategies

A recent DIA working party on adaptive trials stated that manufacturing (API synthesis through to final dose form) needs to be planned 6-18 months before drug is required in the clinic (Nicholls, G *et al*. Managing the drug supply demands of adaptive trial designs (presentation). Substream of DIA Working Party on Adaptive Trial Design, 2012). Modifying manufacturing demand during an adaptive trial, for example by introducing new doses or increasing/decreasing planned sample sizes, can present major challenges and is unfeasible in short term trials. Good up-front planning of manufacturing is therefore essential as changes to plans can be difficult to implement during a trial. We suggest considering the following:

- How many manufacturing campaigns are planned, and how will trial requirements be divided between these? If strategy needs to change, how much lead time is required to implement this? Does the trial duration allow this?
- What are the optimal dose strengths to produce? For example, producing a low unit dose gives most flexibility – but if dose escalation is anticipated, how many units (tablets, capsules, injections) are reasonable for each dose?

Given the lead times associated with manufacturing, while some changes are possible in long-term adaptive trials, we feel that a focus on the packaging of manufactured dose forms gives the greatest potential for efficiencies. For adaptive trials, manufacturing is likely to remain campaign-based as opposed to just-in-time. However, simulation and forecasting, combined with the ability to capture actual demand through IRT, allow the size and outputs of these campaigns to be modified to some extent to manage overages.

Packaging Strategies

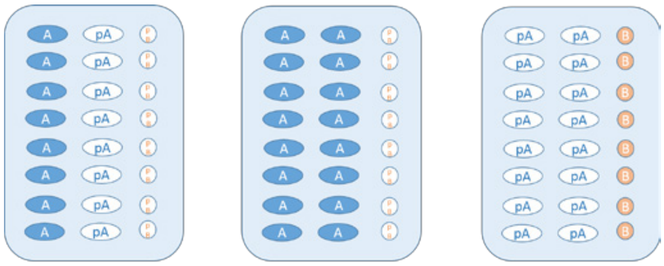
For adaptive trials, packaging strategies should delay commitment of manufactured product and comparator to a dosing regimen or protocol to as late as possible in the supply chain process. At the same time, packaging timelines should still allow the supply chain to react quickly to changes in study design – the DIA working party suggested within one to three days. We also need to ensure that a just-in-time approach to packaging does not result in spiralling production set-up costs. Inevitably, producing smaller batches of product over more operations will result in an increased number of set-ups – however, use of common designs and pooled supplies across programmes can help offset this. We should also consider whether adopting a just-in-time strategy has other impacts. For example, more operations results in more batch releases (e.g. QP release in the EU), so will adopting a just-in-time approach create a bottleneck or increase our resource costs somewhere else in the supply chain?

Where in the Packaging Process do we Implement our Just-in-time Strategy?

Primary Packaging (e.g. Blistering, Bottling, Fill/Finish)

As with manufacturing, primary packaging generally involves the use of automated equipment. Primary packaging lines need to be set up for each batch of material processed, so the more production operations we run, the more set-up costs we incur. It is therefore more cost-effective to produce primary packaged materials in large operations to reduce the impact of set-up fees, and to benefit from the lower unit prices associated with large-scale, high-output packaging lines. In addition, for double-blind clinical trials involving multiple products, a large number of primary packaging steps may be required to produce a patient kit. Does this support the flexibility required for adaptive trial designs?

We recommend continuing to primary package in as few large-volume operations as possible. However, primary packs should be designed with a view to maintaining flexibility if dosing changes. For example, production of mixed-product blister packs is efficient for trials in which doses are likely to



3 treatment groups – A vs 2A vs B. If dosing remains fixed, mixed dose blisters shown are preferable.
- Fewer blistering operations
- Smaller packs (patient convenience, shipping costs)
- Easier/lower cost downstream walleting/carding operations

In an adaptive trial, what happens to blistered drug if the low dose A group is discontinued?
Use of single-product strips would eliminate this waste.

remain fixed. However, if dosing changes in an adaptive trial, do these benefits still hold true? The diagram below illustrates this.

Figure 2: Primary Pack Designs That Offer Benefits in Standard Trials May Lack Flexibility for Adaptive Trials

Similar considerations should be made to other forms of primary pack size and contents. For example, if our clinical experience suggests that we may switch patients to a lower dose over the course of an adaptive trial, do we need to produce prefilled syringes for higher doses, or are we better off giving patients in high-dose groups two doses from a lower-dose prefilled syringe? At the same time, if we are using multiple low doses to make a high dose, at which point does this become undesirable and possibly impact on patient compliance?

Secondary Packaging and Labelling

This part of the supply chain offers the greatest potential for flexibility in terms of meeting the changing requirements of adaptive trials. If dosing changes, label text or kits can be quickly modified to reflect new dosing. It is possible for labels to be developed and kits designed at minimal cost so that design changes can be quickly accommodated if required. If primary packaging employs common, re-usable formats as described above, it is possible to control waste within a trial, and to use the same inventory in other trials in the same programme simply by applying trial-specific information to clinical supplies as late as possible.

There are several ways in which labelling can be used to maximise the flexibility of clinical supplies. We will discuss some examples below.

1. Use of unlabelled primary-packaged materials (brite stock)
In this approach, primary packaged materials are warehoused, and are labelled on demand. Labels for each country, dose level and treatment group are pre-generated and approved, ready to be printed when the decision is taken to initiate a labelling and kit assembly exercise. The trigger to initiate a labelling and assembly exercise can vary:

• **Receipt of an order from an IRT system**
This is true of just-in-time packaging. However, such an approach is not always viable in clinical trials, where timelines may not support generation of batch documentation (and pre-approval if required), room/equipment set-up, label printing and checking, label application and kit assembly, QA/QP release of packed supplies, and shipment to site. In addition, the number of set-up and release fees incurred if such a strategy is employed can be prohibitive.

• **Based on forecast and actual demand at clinical sites**
In this approach a pre-labelled pool of product is produced ahead of receiving IRT orders, the size of which can be determined through simulations. Only a portion of inventory is labelled – the majority of the stock remains unlabelled. Labelled kits are warehoused, ready to be shipped upon receipt of IRT orders. Additional kits are labelled to replace shipped stock as the trial commences, with the aim of always having sufficient kits on hand to meet the demands of the trial. The quantity of labelled kits on hand can be fine-tuned

Figure 3: Comparison of Standard vs Forecast/Demand Based Packaging Strategy

as the trial progresses and the supply chain manager has a better idea of actual as opposed to assumed consumption rates at clinical sites.

This approach can save money by reducing the number of packaging and labelling operations that need to be set up over the course of a study. Producing inventory ahead of orders can generate waste in the event that a study design changes – however, this is significantly lower than waste that can result from pre-packaging and labelling clinical supplies at the beginning of a trial. Figure 3 shows an example of a packaging strategy based on this approach.

Both of the above approaches rely on the use of traditional packaging and labelling operations which must take place in packaging suites. Based on our experience, these are the only approaches that are feasible if primary packs are unlabelled or have no identification marks. We would also advise that the above approaches are used if kits have multiple levels of packaging, this would require kits to be opened to apply labels in a just-in-time manner.

2. Use of part-labelled materials

'Part-labelled' is a slightly misleading term, as these strategies can range from supplies pre-labelled with the bare minimum of information for identification, through to supplies fully labelled with all the information except for the protocol number. The flexibility of supplies and their ability to be re-used in the event that dosing changes depends on the level of detail to which they have been labelled. Supplies labelled with minimal information can be re-used regardless of the changes that happen in the course of the trial. Supplies pre-labelled with booklet labels including dosing instructions may need to be scrapped if re-labelling is not possible. The following approaches open up the possibility of labelling supplies during distribution operations, shortening timelines and eliminating the costs associated with setting up packaging operations.

• Base-labelled supplies
In this approach, primary packs are pre-labelled only with information required to identify and correctly pick packs from storage. Base-labelling is performed in a bulk labelling job immediately after primary production, or may be performed on-line during primary packaging for some pack types (e.g. bottles). In our experience, med ID number/kit number, expiry date (if required) and blinded lot number are typically included on the base label. Med ID number can also be replicated on the label as a barcode/data matrix code to assist in downstream labelling and distribution verification.

Upon receipt of a distribution order from an IRT, the appropriate base-labelled packs are drawn from inventory and issued to a distribution workstation, along with study-specific over-labels. Study-specific over-labels, including all other information required by Annex 13 and local regulations, are applied to kits as part of the distribution process. Distribution paperwork includes the documented process to be followed to support addition of labels during distribution. Manual checks or electronic scanning can be used to ensure the correct labels have been applied to the appropriate packs.

In terms of conserving valuable stock, we feel that this approach offers a strong solution to packaging for adaptive trials. Even if the study design changes and dose groups are dropped, this approach, combined with carefully designed primary packaged components, can restrict waste to only those kits already shipped to site. We have also seen this strategy used as an alternative to booklet labels to maximise supply flexibility in trials requiring multi-lingual labelling. There are limitations to how and when this approach can be used. Our recommendation is that it is used only for trials where there is a single level of packaging in each unit dispensed. For example, a dispensable unit should consist of a bottle, blister, syringe or vial as opposed to a kit containing several items. We have also seen some resistance from QA groups in some companies with regard to labelling in distribution – even when this is controlled as described above.

- **Programme-level pre-labelled kits**

This is a common approach for 'standard' clinical programmes in which sponsors wish to pool inventory across several protocols in the same programme by adding protocol numbers to kits at the point of despatch. Annex 13 allows us to apply some information (e.g. protocol number and expiry date) only to the outer level of packaging. As a result, clinical supplies can be fully packaged and labelled securely in a production room. These are only allocated to a study upon receipt of an order to ship medication to a site, and this is achieved through application of a label including the protocol number at the time of despatch. As with base-labelled supplies, this is controlled procedurally through instructions in the distribution paperwork.

This method does provide some ability to re-use inventory in the event that a trial design changes. It does not offer the same flexibility as the base-labelling approach. If a dose group is dropped from an adaptive study, there could be the opportunity to use this dose in other studies in the same programme. However, if the dropped dose is not in use in alternative studies, drug is wasted. On the positive side, this approach can be applied to trials with more complex kit designs, in which dispensed units consist of multiple levels of packaging.

JIT Supply Chains and Globalisation

The above processes work well when centralised packaging and distribution strategies are utilised. However, clinical trials increasingly include countries in Eastern Europe, Asia and Latin America. To minimise freight costs and transit times, and to minimise the risk of customs delays, inventory is often stored locally in these countries. Since drug is typically stored in distribution-only facilities, how can we maintain supply flexibility through just-in-time labelling? In these circumstances, we would recommend that we maintain a centralised packaging strategy, and supply depots with pre-labelled material only. This is an area where use of simulation and forecasting tools to carefully plan depot inventory levels is essential, as changes to study design can potentially waste not only inventory at clinical sites, but also inventory stored in depots. In addition, sponsors could consider a hub-based distribution strategy (e.g. a single JIT packaging/distribution hub in the US, EU and Asia) for global studies, as opposed to a depot in every country. This will have logistical implications in terms of import/export workload and freight expenses, so the benefits of reduced overage should be weighed up against these competing costs.

Long term, as clinical trials continue to globalise, we anticipate that local capabilities to support in-country just-in-time strategies will grow as sponsors and their clinical supply partners work with depots to implement labelling and kit assembly processes.

Conclusions

Adaptive clinical trials offer significant commercial and ethical benefits to sponsors, regulators and patients. While growing use of adaptive designs will inevitably present increased challenges to the clinical supply chain, these are not insurmountable. As with everything else, planning, communication and early involvement of supply chain stakeholders are the keys to success. There is no one size-fits-all solution – in some cases conserving inventory through smaller, more frequent packaging campaigns is cost-effective. However, for lower-value products we may decide that planning higher overages is a price worth paying for continuity of supply.

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